Summary of Clinical Experiences With Tamsulosin for the Treatment of Benign Prostatic Hyperplasia

Franklin C. Lowe, MD, MPH

Department of Urology, St. Luke's/Roosevelt Hospital Center, New York, NY

Tamsulosin, a uroselective α_{1A}-adrenergic-receptor antagonist, has been shown to improve lower urinary tract symptoms associated with benign prostatic hyperplasia. It has a better side effect profile than earlier α-adrenergic-receptor antagonists, which were initially developed as antihypertensive agents. Clinical trials of 1 year or longer with tamsulosin show high tolerability for the 0.4 mg dose and no significant interaction with other antihypertensive medications.
[Rev Urol. *2005;7(suppl 4):S13–S21*]

Key words: Benign prostatic hyperplasia • Alpha-adrenergic-receptor antagonist • Tamsulosin

Voiding dysfunction associated with benign prostatic hyperplasia (BPH) is very common in aging males. As the "graying of America" continues over the next 2 decades, the prevalence of symptomatic BPH will continue to increase, making BPH an even more important medical and quality-of-life issue. The long-term sequelae and complications of BPH are urinary retention, recurrent urinary tract infections, and obstructive uropathy. More importantly, lower urinary tract symptoms (LUTS), which can dramatically affect an individual's quality of life, will need to be addressed more frequently in the 21st century.

Table 1
Comparison α_1-Adrenergic-Receptor Antagonists

Type	Medication	FDA-Approved Indications	Titratable Required (Yes/No)
Nonspecific	Phenoxybenzamine	Hypertension	Yes
α_1 short-acting	Prazosin	Hypertension	Yes
α_1 long-acting	Terazosin	Hypertension/BPH	Yes
	Doxazosin	Hypertension/BPH	Yes
	Alfuzosin	BPH	No
α_{1A} long-acting	Tamsulosin	BPH	No

Until the 1990s, transurethral resection of the prostate (TURP) was the mainstay of therapy for BPH. In 1987, over 250,000 TURPs were performed in the United States; however, with the advent of effective medical therapies and alternative surgical interventions, the number of TURPs had plummeted to less than 90,000 per year by the year 2000.

Pharmacotherapy has become the generally accepted first line of therapy for LUTS/BPH. Three classes of medical therapies are currently utilized: phytotherapies with uncertain mechanisms of action; 5α-reductase inhibitors, which reduce prostatic volume; and α-adrenergic-receptor antagonists, which decrease smooth muscle tone in the prostatic capsule and bladder neck. In the United States, phytotherapies are obtained by patients via over-the-counter, nonprescription purchase, whereas the other medications must be prescribed by a physician.

Many α-adrenergic-receptor antagonists have been evaluated in the treatment of LUTS; all of these agents were initially developed and approved for the treatment of hypertension, until the development of tamsulosin. Tamsulosin is a more selective α_{1A} subtype antagonist, which maintains the α-antagonist effect on the prostatic capsule and bladder neck but has less of an effect on the vascular system and blood pressure. In fact, tamsulosin is ineffective and not indicated in the treatment of hypertension. Tamsulosin has a favorable side effect profile in regard to problems related to hypotension and dizziness compared to those of terazosin and doxazosin (see Table 1).

Clinical trial experience with tamsulosin, in Europe and in the United States, provided the basis for its approval in 1997 by the U.S. Food and Drug Administration for the treatment of BPH. It will be reviewed herein.

Clinical Experience

Dose Finding Study

The initial study by Abrams and associates[1] was undertaken to help establish the safety and efficacy of tamsulosin, as well as to help determine the optimum dosage for subsequent trials.[2–5]

Initially, 169 patients with symptomatic BPH were enrolled in a 3-week, single-blind placebo run-in period. In this study, 126 patients were eventually randomized to placebo, 0.2 mg, 0.4 mg, or 0.6 mg of tamsulosin once daily for 1 additional month.

Boyarsky symptom scores were improved with all dosages of tamsulosin. The greatest reduction in symptoms occurred in those on either 0.4 mg (-4.1) or 0.6 mg (-4.3), compared to 0.2 (-3.4) and placebo (-2.9). The differences in symptom score improvement were not statistically different between treatment groups because of the small sample size (approximately 30 patients per au). The two highest dosages also provided the greatest improvement in peak urinary flow rates Q_{max} compared to placebo, with improvements of 2.2 and 2.4 mL/sec for the 0.4 mg and 0.6 mg dosages, respectively.

In 1987, over 250,000 TURPs were performed in the United States; however, the number of TURPs had plummeted to less than 90,000 per year by the year 2000.

Three-Month Studies

Several 3-month, multicenter, randomized, placebo-controlled trials evaluating the safety and effectiveness of tamsulosin for the treatment of BPH/LUTS were conducted in Europe and the United States (see Tables 2 and 3). The studies conducted in Europe were reported by Abrams and colleagues[2] and Chapple and colleagues.[3] The US studies were reported by Lepor[4] and by Narayan and Tewari.[5]

In the Abrams study,[2] 313 men with moderate symptoms of BPH (Boyarsky symptom scores 6 or higher and peak urinary flow rates

Table 2
Safety of Tamsulosin Therapy in Short-Term Placebo-Controlled Studies

	Patients No.	% Discontinuation due to adverse events		% Dizziness (AR)		% Abnormal ejaculation (AR)	
Abrams et al[2]	296	T	4.1	2.5	(0.5)	4	(3)
		Placebo	3.1	2.0		1	
Abrams et al[1]	126	T 0.4	3	7.0	(7)	0	(0)
		Placebo	7			0	
Chapple et al[3]	575	T	4.5	3.4	(0.3)	4.5	(3.5)
		Placebo	3.6	3.1		1	
Lepor et al[4]	756	T 0.4	NR	10	(5)	6	(6)
		T 0.8	NR	11	(6)	18	(18)
		Placebo	NR	5		0	
Narayan et al[5]	735	0.4	9	20	(5)	11	(10)
		0.8	12	23	(8)	18	(17)
		Placebo	8	15		1	

AR, Attributable Risk of tamsulosin vs placebo.

between 4 and 12 mL/sec) were entered in the study and received either tamsulosin 0.4 mg once daily or placebo for 12 weeks. During the 2-week single-blind placebo run-in phase, 17 subjects were withdrawn from the study. Eventually, 296 men were randomized in a 2:1 ratio between tamsulosin 0.4 mg and placebo. At the end of the study, 281 patients were evaluable, 187 tamsulosin-treated, and 94 placebo-treated. After randomization, 20 patients failed to complete the study because of lack of efficacy (3) side effects (11), or administrative reasons (6).

Objective parameters studied included Boyarsky symptom scores and peak urinary flow rates. Boyarsky symptom scores improved by an average of 3.4 units (36% reduction from baseline) and 2.2 units (24% reduction) in tamsulosin-treated and placebo-treated patients, respectively. Also noted was a more than 25% decrease in Boyarsky symptom scores in 67% of tamsulosin-treated patients, compared to only 44% of placebo-treated patients ($P < .001$). Peak urinary flow rates improved by 1.4 mL/sec for tamsulosin-treated patients and by 0.4 mL/sec for placebo-treated patients ($P < .05$).

In terms of safety, side effects were noted in 34% and 24% of tamsulosin-treated and placebo-treated patients, respectively. It is of note that the incidence of cardiovascular-related side effects in the two groups was comparable at 5% and 7%, respectively. No significant changes in blood pressure or vital signs were noted in either group, nor were there significant differences in blood pressure or vital signs between groups.

Chapple and colleagues[3] reported on the combined analysis of two multicenter European studies that followed the same design: a 2-week single-blind placebo run-in period followed by 2:1 randomization to either tamsulosin 0.4 mg daily or placebo for 12 weeks. Of the 627

Table 3
Efficacy of Tamsulosin Therapy in Short-Term Placebo-Controlled Studies

	Patients No.	Duration (months)	Dosages (mg)	ΔQ_{max} (cc/sec)	Δ Symptom score	% Δ
Abrams et al[2] 1995	296	3	0.4	+1.4*	-3.4[B*†]	-36%
Abrams et al[1] 1997	126	1	0.4	+2.2*†	-4.1[B]	-29%
Chapple et al[3]	575	3	0.4	+1.6*†	-3.3[B*†]	-35%
Lepor et al[4]	756	3	0.4/0.8	+1.8*†	-8.3[A]	-42%
			0.4	+1.8*†	-9.6[A]	-48%
			0.8			
Narayan et al[5]	735	1	0.4/0.8	+1.5 (not statistically different)	-5.1[A*†]	-25%
			0.4		-5.8[A*†]	-25%
			0.8	+1.8*†		

B = Boyarsky score
A = AUA symptom score
* $P < .05$; † $P < .01$

men who entered in the study, 575 were eventually randomized; 382 were treated with 0.4 mg tamsulosin and 193 received placebo. Of these, 535 completed the 12-week treatment phase, with 7% (25) of the tamsulosin-treated and 8% (15) of the placebo-treated patients discontinuing the trial. The reasons for discontinuation—side effects (4%), lack of therapeutic response (1%), and administrative reasons (2%)—were similar in the groups.

No tamsulosin-treated patient had first-dose syncope.

Boyarsky symptom scores (scale 0–27 points) improved by 3.3 units (35% reduction) and 2.4 units (26% reduction) for the treatment and the control group, respectively (P = .002). A reduction in symptoms from baseline of more than 25% was noted in 66% and 49% of tamsulosin- and placebo-treated patients, respectively (P < .001). Peak urinary flow rates improved by 1.6 mL/sec and 0.6 mL/sec, respectively, for the tamsulosin and placebo-treated groups (P < .002).

The incidence of any side effects was 36% for tamsulosin-treated patients and 32% for placebo-treated patients. Drug-related side effects were also comparable, at 13% for patients taking tamsulosin and 12% for those taking placebo. Dizziness was noted in 3% of each group. Postural hypotension and syncope was noted in only 1 tamsulosin-treated patient. Additionally, vital sign monitoring showed no significant changes in supine or standing blood pressure monitoring compared to placebo.

In the United States, Lepor and colleagues[4] completed a similar multicenter, placebo-controlled, double-blind trial. Eligibility requirements included an American Urological Association (AUA) symptom score (scale 0–35 points) ≥ 13 and a peak urinary flow rate between 4 and 15 mL/sec. After a 1-week placebo run-in, 756 patients were equally randomized to either 0.4 mg tamsulosin, 0.8 mg tamsulosin, or placebo for 12 weeks. Patients randomized to 0.8 mg received 0.4 mg of tamsulosin for 1 week before dose escalation occurred. A total of 618 patients completed the trial; of the 138 patients who did not complete the study, 71 prematurely terminated their participation due to side effects.

Effective response criteria for the study were defined as more than a 25% improvement in AUA symptom score and more than a 30% improvement in peak urinary flow rate. An improvement of more than 25% in symptom score was noted in 70% of the 0.4 mg-, 74% of the 0.8 mg-, and 51% of the placebo-treated patients. Mean increases in peak urinary flow rates were 1.75, 1.79, and 0.52 mL/sec for the 0.4 mg, 0.8 mg, and placebo groups, respectively. An improvement in peak urinary flow of more than 30% was seen in 31% and 36% of the 0.4 mg- and 0.8 mg-tamsulosin-treated patients, respectively, but in only 21% of the placebo-treated patients. Although the onset of improvement in peak flow was recorded after the first dose of tamsulosin, maximum improvements in peak urinary flow rates were achieved by the end of the first week of therapy.

In the Narayan and Tewari study,[5] patients with moderate to severe BPH symptoms were evaluated after a 1-month single-blind placebo run-in. Of the 1476 evaluated, 735 were randomized equally to 0.4 mg tamsulosin, 0.8 mg tamsulosin, or placebo. There was statistically significant improvement from baseline in AUA symptom scores in tamsulosin-treated patients: 5.1 units for the 0.4 mg and 5.8 units for the 0.8 mg group (P = .01). Notably, no statistical difference in the total AUA symptom score improvement was shown between the 0.4 mg and the 0.8 mg groups. The percentage and number of patients who demonstrated a reduction from baseline of more than 25% in AUA symptom score were 55% (133/244), 56% (134/238), and 40% (95/235) for the 0.4 mg, 0.8 mg, and placebo groups, respectively (P = .01).

Peak urinary flow rates improved by 1.52 mL/sec for 0.4 mg-, 1.79 mL/sec for 0.8 mg-, and 0.93 mL/sec for placebo-treated patients. Only the improvement with the 0.8 mg dose was statistically greater than that with placebo (P = .007). The percentage of patients with a 30% or more improvement in peak urinary flow rate over baseline was 34% for 0.4 mg, 33% for 0.8 mg, and 24% for placebo. The results for both tamsulosin-treated groups were statistically significant compared to those for placebo (P < .05); the difference between the two tamsulosin-treated groups was not significant.

Tamsulosin has become the α-adrenergic-receptor antagonist most commonly prescribed by urologists for BPH in the United States.

Extensive analyses of side effects and safety were undertaken. Side effects were noted in 49%, 53%,

and 51% of the 0.4 mg, 0.8 mg, and placebo groups, respectively. Dizziness, somnolence, and rhinitis were comparable between the 0.4 mg and placebo groups; however, their incidence was statistically significantly greater than that seen with placebo versus the 0.8 mg group. Both tamsulosin groups had significantly greater incidence of altered ejaculation—11% and 18% for the 0.4 mg and 0.8 mg groups, respectively—than the placebo group, with less than 1%. The most common reason for withdrawal from the study was dizziness, with 2%, 4%, and 2% for the 0.4 mg, 0.8 mg, and placebo groups, respectively.

In terms of cardiovascular issues, no tamsulosin-treated patient had first-dose syncope. No clinically significant changes in systolic or diastolic blood pressure or in orthostatic monitoring were noted.

One-Year Studies

Lepor and associates conducted a 40-week, open label extension of the previously reported 13-week trial.[4] Of the 618 subjects who completed the initial phase, 418 (68%) enrolled in the extension phase.[6] During this trial, discontinuation rates due to side effects were 5% for 0.4 mg, 16% for 0.8 mg, and 6% for placebo-treated patients.

The mean changes from baseline in AUA symptom scores were 9.4 units, 9.7 units, and 6.5 units for the 0.4 mg, 0.8 mg, and placebo-treated groups, respectively (Figure 1). The percentages of patients responding in terms of AUA symptom improvement were 81%, 78%, and 59% for the same respective groups, in which peak urinary flow rates improved by 1.7, 2.1, and 0.4 mL/sec. Only the tamsulosin-treated groups had statistically significant improvement over baseline.

Side effects were again greater in the 0.8 mg group than in either the 0.4 mg or the placebo group. The 0.4 mg tamsulosin and placebo group side effect profiles were comparable except for abnormal ejaculation, which had an incidence of 10% with tamsulosin 0.4 mg versus 0% for placebo. The 0.8 mg group had a 26% incidence of abnormal ejaculation. Cardiovascular side effects were 14%, 10%, and 14% for the placebo, 0.4 mg, and 0.8 mg tamsulosin groups, respectively.

Schulman and colleagues[7] reported on 244 patients who continued on 0.4 mg of tamsulosin for an additional 60-week extension after participation in an earlier 3-month trial.[2] This open label extension trial documented sustained improvements in Boyarsky symptom score and peak urinary flow rate over its duration. The discontinuation rate due to side effects was 8%. Dizziness and abnormal ejaculation were reported in 5.7% and 5.3%, respectively, of the patients treated with 0.4 mg.

Postmarketing Observation Studies

The results from two observational postmarketing surveillance studies of 9507 and 9858 men treated with tamsulosin in Germany demonstrated excellent tolerability among all groups of patients (those with and without comorbidities and those with and without concomitant cardiovascular drug use).[7] Ninety-four percent of patients in one study and 97% of those in the other reported either good or very good tolerability. Patients with concomitant disease (diabetes, hypertension, coronary artery disease) reported a slightly poorer tolerability than those without it ($P < .05$), but global tolerability was still rated as good or very good in more than 90% of patients questioned in one study and 95% of those in the other.

Michel and colleagues also addressed the issue of interaction with other cardiovascular medications (Table 4).[8] There was no difference in tolerability between groups in Study 1, or for those on β-blockers in Study 2. However, in Study 2 those being concomitantly treated with diuretics, calcium channel blockers, or angiotensin-converting enzyme inhibitors reported a slightly lower tolerability ($P < .05$) but still had a favorable global tolerability of 95%.

Blood pressure monitoring was also conducted in those 19,000 tamsulosin-treated patients (Table 5).[8] After 12 weeks of therapy, systolic and diastolic blood pressures were 3.6 and 1.7 mm Hg lower, respectively, than they were before treatment for controls, which is comparable to the effects noted for placebo in prior trials. Mean additional blood

Table 4
Tolerability of Tamsulosin in 19,365 Patients at End of Therapy*

Tolerability	Study 1 (n = 9507), 4 weeks	Study 2 (n = 9858), 12 weeks
Very good	53.1% } > 93.8%	58.8% } > 97.5%
Good	40.7%	38.7%
Moderate	3.6%	1.6%
Poor	2.6%	1.0%

*Data from Michel et al.[8]

pressure reductions in patients on concomitant antihypertensive therapy were not more than 2 mm Hg. These monitoring studies confirmed the previously reported lack of significant interaction when tamsulosin is coadministered with other α-adrenergic-receptor antagonists given to treat hypertension.[9]

Clinical Usage

Over the last 4 years, tamsulosin has become the α-adrenergic-receptor antagonist most commonly prescribed by urologists for BPH in the United States due to several factors:

1. No need for titration because α_{1A} selectivity prevents blood pressure alterations
2. Rapid onset of response, because the initial dose of 0.4 mg is a therapeutic dose
3. No need to alter concomitantly taken antihypertensive medications
4. Fewer cardiovascular side effects (dizziness, asthenia, orthostatic hypotension) than either terazosin or doxazosin

The overall efficacy of the various α-adrenergic-receptor blockers appears to be comparable,[10] although analysis of the various studies with different patient populations having different baseline severity of symptoms, using different protocols, and showing variable placebo response rates, adds to the uncertainty of the comparison. However, the more problematic side effect profiles of the nonselective α-adrenergic-receptor blockers have had a significant impact upon utilization. The higher incidence of cardiovascular and dizziness-related symptoms experienced with terazosin and doxazosin have provided greater impetus for tamsulosin use.

In general, the 0.4 mg dose of tamsulosin is the optimal one. There are greater side effects when the dose is escalated to 0.8 mg, with only marginal improvements in symptom scores and peak urinary flow rates.[5]

Comparison of Side Effects With Other α-Blockers

Tamsulosin causes fewer side effects resulting in discontinuation from short-term clinical trials than either terazosin (5.9%–15%) or doxazosin (10%–14%).[10,11] Discontinuation of tamsulosin-treated patients was comparable to placebo, with an attributable drug effect of only 1% for a 0.4 mg dose.[11]

The most common side effect noted with α-blockers utilized for the treatment of LUTS/BPH is dizziness.[10,11] The attributable drug effect incidence of dizziness was 10%–20% for doxazosin and 5%–10% for terazosin in placebo-controlled trials. Although dizziness was also the most common side effect of tamsulosin therapy noted in placebo-controlled trials, its attributable drug effect was only 0.3%–5% for a 0.4 mg dose. This reduction of both dizziness and side effects in general with tamsulosin is

Figure 1. (A) *Change in mean ± SD total American Urological Association symptom score from baseline and* (B) *change in mean ± SD maximum urinary flow from baseline. Both baselines established at first double-blind dose in phase III trial to the endpoint of the extension phase (53 weeks of double-blind therapy). Reproduced and adapted with permission from Lepor et al.*[6]

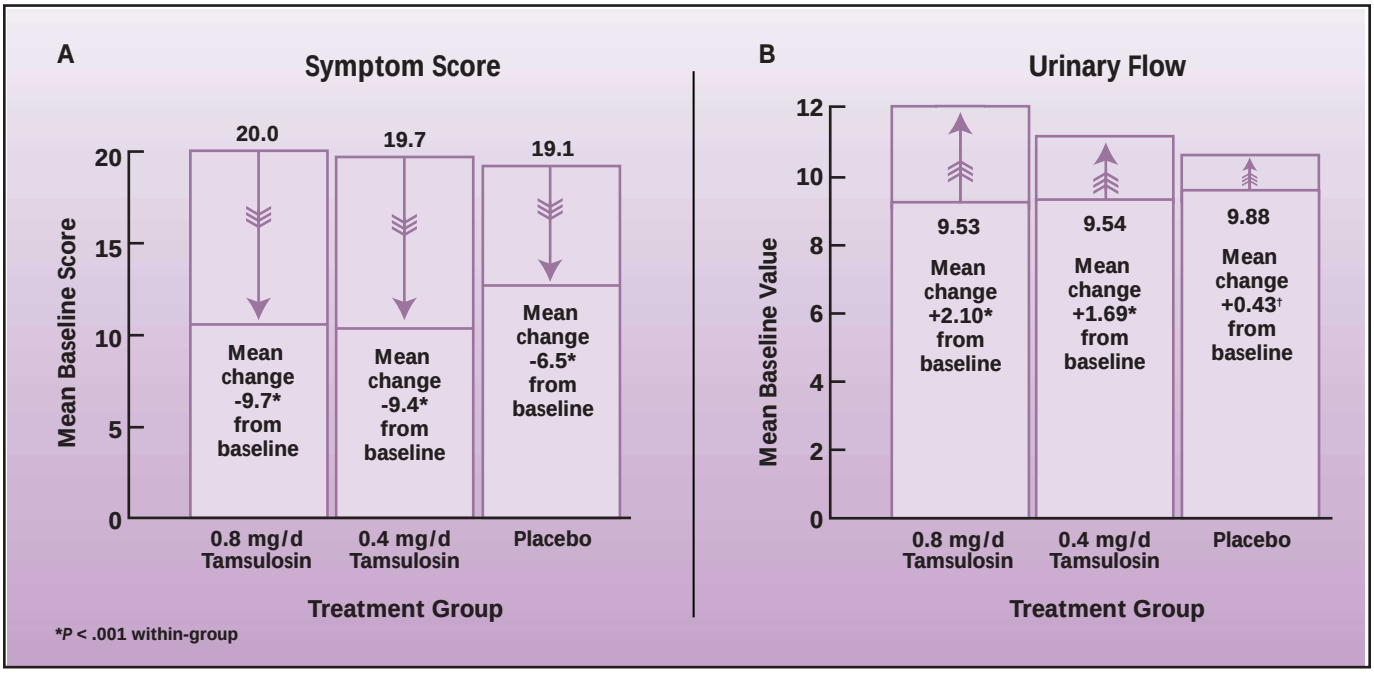

Table 5
Effects of Comorbidities on Blood Pressure in Tamsulosin Therapy

Patient Subgroup	Baseline Systolic (mm Hg)	Baseline Diastolic (mm Hg)	Posttherapy Change Systolic/Diastolic (mm Hg)
Control	141 ± 0.2	84 ± 0.1	–3.6 ± 0.2/–1.7 ± 0.1
	(n = 4393)		(n = 4218)
Diabetes	150 ± 0.5	89 ± 0.3	–4.7 ± 0.4/–2.9 ± 0.3
	(n = 1162)		(n = 1109)
Hypertension	154 ± 0.4	91 ± 0.2	–5.2 ± 0.3/–3.5 ± 0.2
	(n = 1749)		(n = 1673)
Other cardiovascular	150 ± 0.4	89 ± 0.2	–4.3 ± 0.3/–2.8 ± 0.2
	(n = 1638)		(n = 1569)

Data from Michel et al.[8]

likely due to its greater α-$_{1A}$ subtype affinity, relative to α-$_{1B}$.

In the two pivotal, 3-month, placebo-controlled trials conducted in the United States,[4,5] extensive evaluation and monitoring of vital signs, blood pressure, and orthostatic changes were undertaken.[12] (See Table 6). Tamsulosin had minimal effects on blood pressure, compared to placebo; attributable drug effect was 2.3 mm Hg for the 0.4 mg dose and 4.1 mm Hg for the 0.8 mg dose of tamsulosin, compared to placebo. Sub-group analyses of normotensives, controlled-hypertensives, and uncontrolled hypertensives showed that baseline blood pressure status was inconsequential for alterations in either systolic or diastolic blood pressure.[12]

Extensive orthostatic monitoring of tamsulosin was performed because the older non-selective α-blockers are all plagued with problems of first dose effect of syncope and orthostasis. Therefore those α-blockers (phenexybenzamine, doxazosin, and terazosin), which were initially approved for the treatment of hypertension, required titration in order to prevent these problems. These studies documented that an effective dose of tamsulosin could be administered without titration. There were no clinically significant first dose effects in these trials.

The overall incidence of symptoms indicative of orthostasis (symptomatic postoral hypotension, syncope, or vertigo) was 1.4%. Only 0.2% (1/502 patients) treated with 0.4 mg of tamsulosin experienced symptomatic postural hypotension (see Table 7). Additionally, only 0.4% (2/491 patients) on 0.8 mg of tamsulosin had symptomatic postural hypotension. Amazingly, only 1 in 993 tamsulosin-treated patients had orthostatic symptoms and systolic blood pressure reduction of greater than 20 mm Hg.

Only recently was a large prospective comparison trial between tamsulosin and terazosin completed.[13] In this study, 1983 men were randomized to

Table 6
Criteria for Orthostatic Test Data

1. SBP decrease of 20 mm Hg from supine to standing
2. DBP decrease of 10 mm Hg on standing and a standing DBP < 65 mm Hg
3. Pulse rate increase of 20/min on standing and a standing pulse rate of 100/min
4. Clinical symptoms on standing (faintness, light-headedness, dizziness, spinning sensation, vertigo, or postural hypotension)

POSITIVE RESULT
Patients satisfying at least one of the four criteria = positive orthostatic result.
Patients satisfying both criteria (1) and (4) at a given visit = clinically significant orthostatic hypotension.
Patients satisfying all four criteria.

SBP, systolic blood pressure; DBP, diastolic blood pressure.
Reprinted from Narayan et al[12], with permission.

Table 7
13-Week Orthostatic Test Results

	Tamsulosin 0.4 mg	Tamsulosin 0.8 mg	Placebo
SBP decrease	11.2% (56/502)	13.0% (64/491)	8.9% (44/493)
DBP decrease	2.0% (10/502)	3.7% (18/491)	0.8% (4/493)
Heart rate increase	5.0% (25/502)	4.5% (22/491)	1.6% (8/493)
Clinical symptoms	0.2% (1/502)	0.2% (1/491)	0.0% (0/493)
Total positive Test result	16.1% (81/502)	18.7% (92/491)	11.0% (54/493)
SBP decrease + symptoms	0.0% (0/502)	0.2% (1/491)	0.0% (0/493)

Reprinted from Narayan et al[12] with permission.
DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 8
Treatment-Emergent Adverse Events Reported in ≥ 5% of Patients

	Tamsulosin 0.4 mg n = 1002	Terazosin 5 mg n = 981
Fatigue	25 (2.5%)	53 (5.4%)*
Dizziness	55 (5.5%)	119 (12.1 %)*
Rhinitis	55 (5.5%)	61 (6.2%)

*$P < .001$

either tamsulosin 0.4 mg or to terazosin 5 mg. The terazosin was titrated from 1 mg to 5 mg and followed for 8 weeks of therapy. The overall discontinuation rate for the trial due to side effects was 4.3% for tamsulosin and 6.6% for terazosin; the most common cause for discontinuation was dizziness (0.6% for tamsulosin and 2.0% for terazosin).

The overall incidence of side effects was comparable between the two medications: 54% for tamsulosin and 56% for terazosin. However, both dizziness and fatigue were more than double in the terazosin-treated patients. (see Table 8).

Additionally, serious adverse events occurred in 21 terazosin- and 13 tamsulosin-treated patients. Of these, 3 out of 21 were considered related to the study medication terazosin, and none of the 13 were considered related to tamsulosin.

Direct comparison, in regard to cardiovascular adverse events, showed that tamsulosin 0.4 mg caused two (0.29%) episodes of hypotension compared to seven (0.7%) with terazosin. No tamsulosin-treated patients had either syncope or postural hypotension. Thus, the direct comparison trial confirms that dizziness, fatigue and hypotension are more common with terazosin.

Summary

The development of tamsulosin, a more selective α_{1A}-adrenergic-receptor antagonist, has provided clinicians with an efficacious, safe, and well-tolerated therapeutic option for the treatment of LUTS associated with BPH. Its favorable side effect profile

Main Points

- Pharmacotherapy has become the generally accepted first line of therapy for lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH).
- Until the development of tamsulosin, all α-adrenergic-receptor antagonists used to treat LUTS were initially developed and approved for the treatment of hypertension.
- Tamsulosin, a selective α_{1A}-adrenergic-receptor antagonist, maintains the α-antagonist effect on the prostatic capsule and bladder neck without major effects on the vascular system and blood pressure.
- A dose of 0.4 mg is optimal for clinical practice.
- Its α_{1A} selectivity allows tamsulosin to allay symptoms of BPH without altering blood pressure; the drug was effective and well tolerated in trials lasting 1 year or more.
- Tamsulosin has no significant interaction with other commonly prescribed antihypertensive therapies.

compared to those of the earlier α-adrenergic-receptor antagonists, which were initially developed as antihypertensive medications, has spurred its use in clinical practice. The 0.4 mg dose is optimal for clinical practice; there is little additional benefit from using the 0.8 mg dose. ■

References

1. Abrams P, Speakman M, Stott M, et al. A dose-ranging study of the efficacy and safety of tamsulosin, the first prostate-selective alpha 1A-adrenoceptor antagonist, in patients with benign prostatic obstruction. *Br J Urol*. 1997;80:587–596.
2. Abrams P, Schulman CC, Vaage S. Tamsulosin, a selective alpha 1c-adrenoceptor antagonist: a randomized, controlled trial in patients with benign prostatic "obstruction" (symptomatic BPH). The European Tamsulosin Study Group. *Br J Urol*. 1995;76:325–336.
3. Chapple CR, Wyndaele JJ, Nordling J, et al. Tamsulosin, the first prostate selective alpha-1A adrenoceptor antagonist: a meta-analysis of two randomized placebo-controlled multicentre studies in patients with benign prostatic obstruction. *Eur Urol*. 1996;29: 155–167.
4. Lepor H, for the Tamsulosin Investigator Group. Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. *Urology*. 1998;51:892–900.
5. Narayan P, Tewari A, and US 93-01 Study Group. A second phase III multicenter placebo controlled study of 2 dosages of modified release tamsulosin in patients with symptoms of benign prostatic hyperplasia. *J Urol*. 1998;160:1701–1706.
6. Lepor H. Long term evaluation of tamsulosin in benign prostatic hyperplasia: a placebo controlled, double-blind extension of a phase III trial. *Urology*. 1998;51:901–906.
7. Schulman CC, Corturiend J, Jonas U, et al. Tamsulosin, the first prostate selective alpha-1A adrenoceptor antagonist: analysis of a multinational multicenter open-label study assessing the long-term efficacy and safety in patients with benign prostatic obstruction. *Eur Urol*. 1996;29:145–154.
8. Michel MC, Mehlburger L, Bressel HU, et al. Tamsulosin treatment in 19,365 patients with lower urinary tract symptoms: does co-morbidity alter tolerability? *J Urol*. 1998;160:784–791.
9. Lowe FC. Coadministration of tamsulosin and three anti-hypertensive agents in patients with benign prostatic hyperplasia: pharmacodynamic effects. *Clin Ther*. 1997;19:730–742.
10. Djavan B, Marberger M. A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urology*. 1999:36:1–13.
11. Lowe FC. Alpha-1-adrenoceptor blockade in the treatment of benign prostatic hyperplasia. *Prostate Cancer and Prostatic Disease*. 1999;2:110–119.
12. Narayan P, Lowe FC. The effects of tamsulosin on vital signs in two multicenter, placebo-controlled studies. *Cardiovascular Reviews and Reports*. 2000;21:494–499.
13. Lowe F, Djavan B. Prospective, randomized trial to evaluate the side effect profile of tamsulosin vs terazosin in 1983 men with benign prostatic hyperplasia. *J Urol*. 2002;167: 267 [Abstract].

Editor's Summary of Meeting Presentation

Dr. Frank Lowe reviewed the pivotal trials conducted in the United States and Europe examining the safety and effectiveness of tamsulosin for the treatment of BPH. The discussion following the presentation focused on tamsulosin's unique mechanisms of action and the optimal tamsulosin dose.

It was generally agreed that tamsulosin exhibits only modest pharmacologic selectivity for the α_1 AR subtypes. Specifically, tamsulosin's selectivity for the α_1 and α_{1D} versus α_{1B} subtype is only 10-fold, and there is no subtype selectivity between α_{1A} versus α_{1D}. The panel questioned whether this modest selectivity translates into any clinical relevance. The factor most likely responsible for tamsulosin's unique clinical properties is its slow release formulation, which virtually eliminates an effect on blood pressure and allows for the administration of a clinically effective and very well tolerated dose without the requirement for dose titration.

There was general agreement that the effectiveness and side effects associated with all α_1-blockers including tamsulosin are dose dependent. The 0.4 mg dose of tamsulosin is extremely well tolerated and its side effect profile is almost equivalent to placebo. Increasing the dose of tamsulosin to 0.8 mg increases the likelihood of side effects, such as retrograde ejaculation and dizziness. It was generally felt that the modest increase in effectiveness of the 0.8 mg dose was overshadowed by the increase in adverse events. Another practical issue is that a 0.8 mg dose is not commercially available. Therefore, the cost of administering 0.8 mg of tamsulosin is twice that of 0.4 mg. On the basis of effectiveness, tolerance, cost, and convenience, the entire panel agreed that 0.4 mg of tamsulosin is the preferred dose. Prescribing patterns suggest that 90% of physicians prescribe 0.4 mg of tamsulosin. The higher doses are generally reserved for those men who fail to respond to 0.4 mg.